N2 GUIDANCE
FOR
HEALTH CANADA INSPECTIONS

Supporting Investigators and Sponsor-Investigators in the preparations for a Health Canada Inspection

Version: 30-Jan-2023

ROLES TO SUPPORT A SITE INSPECTION

Sponsor-Investigator or Qualified Investigator (QI): Responsible for ensuring that the study site and all team members are prepared to participate in audits or regulatory inspections, as required. Some parts of audit/inspection preparation may be delegated to appropriately trained study team members, but remain the ultimate responsibility of the Sponsor-Investigator or Qualified Investigator (QI)/Investigator.

Manager, Clinical Research: Responsible for attendance and participation at the opening and closing meetings as well as answering questions in a forthright and honest manner during the conduct of the audit. Works in conjunction with the Research Compliance and Ethics Manager (Compliance) to assign roles to support the efficient conduct of the audit/inspection. Also responsible for notifying Sponsor and/or CRO of inspection, as applicable and scheduling time and date with inspector (if allowed).

Quality Assurance/Research Compliance: Responsible for ensuring all relevant personnel are trained on the conduct of audit/inspections as they pertains to their roles. Includes the development and maintenance of SOPs, work plans, and support documentation prior to the audit/inspection. Where possible, will be the Inspection Facilitator in regulatory inspections as detailed in this SOP. Responsible for development, as required by the auditor/inspector, and tracking of any Corrective Action Preventive Actions (CAPAs) resulting from the audit/inspection.

Research Coordinator/Assistant: Responsible for attending and participating in all aspects of the audit/inspection as requested, a primary resource for the auditor/inspector, providing documents, answering questions in a forth-right and honest manner, and following up, as required, to address auditor/inspector findings and taking corrective actions as mandated by the auditor/inspector.

Research Administrative Assistant: Responsible for maintenance of the Inspection Readiness kit located in reception of the Research and Capacity Building department, as detailed in this SOP.

Inspection Facilitator: Responsible for managing the overall audit / inspection process on behalf of the inspection site.

Document Controller: Responsible for retrieving and copying requested documents and maintaining a log of documents provided to the auditor / inspector.

Scribe (where required): Responsible for keeping detailed minutes during the audit / inspection, usually opening/closing meetings with the auditor / inspector, and any interviews of personnel by the auditor / inspector.

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GUIDANCE DOCUMENT AND PRE-INSPECTION PREPARATION CHECKLIST FOR HEALTH CANADA INSPECTION

INTRODUCTION

The following guidance document and preparation checklist has been prepared by the N2 Quality Committee. It is designed to help Sponsor-Investigators, Qualified Investigators and their research teams prepare for a Health Canada inspection. If you are a Sponsor, please refer to ICH Good Clinical Practice for additional inspection preparations. Resources from Health Canada, N2 SOP17-09 Audits and Inspections, member institutions and experience with relation to both Sponsor and site inspections have been used. The views expressed in this document are those of the N2 Quality Committee.

HEALTH CANADA'S REGULATORY OPERATIONS AND ENFORCEMENT BRANCH (ROEB) – CLINICAL TRIAL COMPLIANCE PROGRAM (CTCP)

Health Canada
Regulatory Operations and Enforcement Branch

a. Medical Devices and Clinical Compliance
b. Clinical Compliance, Border Operations and Canada Vigilance
c. Clinical Trial and Biological Product Compliance
    i. Biological Product Compliance
    ii. Clinical Trial and Biological Product Compliance
    iii. Clinical Trial Compliance

Guidance

Health Canada's ROEB performs inspections of Health Canada-regulated clinical drug trials. As per Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects": GUI-0100, page 89 Health Canada defines a clinical trial as "an investigation in respect of a drug for use in humans that involves human participants and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug". Inspections are performed to assess compliance with the Food and Drug Regulations, Division 5 - "Drugs for Clinical Trials involving Human Participants", ICH E6 - Good Clinical Practices (GCP) and other pertinent guidelines.

Health Canada may inspect Sponsors, clinical trial sites, Contract Research Organizations (CROs) and Site Management Organizations (SMOs). The ROEB Inspectorate conducts approximately 80 inspections each year across Canada (goal is up to 2% of all Canadian clinical trial sites per year). Inspections are conducted during the active phase of a clinical trial or after the completion of a clinical trial.

SELECTION OF SITES FOR INSPECTION

The selection of clinical trials for inspection is based on risk-based criteria, including but not limited to:

- The phase in the drug development process
- Clinical trial design - trial objectives, complexity, blinding, size, trial endpoints
- Participant population
- Novel therapies / type of drug
- Dosage forms i.e., injectable, intraventricular, subcutaneous
- Indication for drug(s) used in the trial
- Marketed drug for a new indication
- Significant or frequent reports of serious adverse drug reactions
- Notices from Sponsors of protocol deviations

From lists of identified studies, the Inspectorate requests site information from Sponsors, including:

- Location of each site
- Name of each Qualified Investigator (QI)
- Status of the study i.e., not yet enrolling, dosing, in follow up, closed
- Number of participants enrolled, active and withdrawn
- Number of serious unexpected adverse drug reactions at the clinical trial site or other sites
- Parties involved i.e., Industry Sponsor, CRO, SMO, etc.

The Inspectorate may also request information directly from the site QI and/or institutional representative. The site QI may be asked to complete a "**Clinical Trial Information Request Form**" (*See Appendix 2 – Clinical Trial Information Request Form*).

The Inspectorate then uses criteria, including the following, to make the final selection of sites for inspection:

- Type of site i.e., located at large institution vs. small clinic
- Geographic location i.e., sites selected throughout the region
- Number of clinical trials conducted at the site
- Inspection history of the QI and Sponsor including observations made during past inspections
- Regional concerns / priorities

The choice of inspection sites will also be reviewed periodically in consultation with the Therapeutic Products Directorate (TPD) and the Biologics and Radiopharmaceutical Drugs Directorate (BRDD) of the Health Products Food Branch (HPFB). During Health Canada's review of a Clinical Trial Application (CTA), the Medical Reviewers apply the risk factor criteria to the study protocol. Clinical trials deemed as higher risk may be flagged for inspection.

INSPECTION OBJECTIVES

1) Ensure the protection of enrolled participants
2) Verify compliance to Division 5 of the Regulations
3) Ensure that the generally accepted principles of good clinical practices are met
4) Validate the quality of the data generated
5) Investigate complaints

Note: Where there are differences between Division 5 and ICH GCP, e.g. record retention period, Division 5 takes precedence.

INSPECTION PROCEDURES

Most inspections are conducted as announced inspections. Notification is usually sent to the Sponsor and the site a minimum of 5 days (up to 4 weeks) before the inspection is conducted. Inspections may also be conducted unannounced at the discretion of Health Canada.

The inspection visit is usually scheduled for a minimum of five (5) business days however it may be conducted over a longer period, if necessary. During the routine inspection visit, the Health Canada Inspectors will conduct interviews with research personnel and review regulatory and study documentation. Following the visit, the Health Canada Inspector will issue the **Inspection Exit Notice**.
Remote inspection visits are scheduled for up to ten (10) business days.

HPFB INSPECTORATE INSPECTION

A Health Canada Inspector may initiate compliance and enforcement activities when potential non-compliance or risk has been identified. Where non-conformity to the Regulations is verified a risk based approach is taken to bring the regulated party into compliance using tools such compliance promotion and monitoring, and enforcement. See Health Canada's *Compliance and enforcement policy for health products* (POL-0001) for examples. Inspection results may be communicated to TPD or BRDD with the information needed to determine recommendations regarding the suspension of authorization and the assessment of the validity of submitted data.

In extreme cases of non-compliance Health Canada may initiate an investigation under the Criminal Code of Canada. With limited exceptions the powers of inspectors as granted under the Act do not apply in these circumstances.

PREPARING THE SITE FOR A HEALTH CANADA INSPECTION

Notification Process Guidance

Once Health Canada selects a clinical trial site, the Health Canada Inspector may contact the QI by phone or email initially to arrange a time for the inspection visit. Whenever possible, allow an adequate amount of time for all parties to prepare for the inspection prior to the visit. Subsequent correspondence between Health Canada and the QI and/or the Sponsor is usually made by email.

Following the initial notification, the Health Canada Inspector will send the site QI and the Sponsor an official **Notice of Inspection Letter** (by email and/or hard copy). In preparation for the inspection, Health Canada recommends the review of the following documents that can all be found at:

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html

- Health Canada, Food and Drug Regulations, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects, (Schedule 1024), June 20, 2001.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2), November 9, 2016.
- Health Canada, Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects", GUI-0100, August 20, 2019.
- Health Canada, Guidance Document: "Classification of observations made in the conduct of inspections of clinical trials", GUI-0043, August 29, 2008.

The Notice of Inspection Letter may include a copy of Health Canada's 'Good Clinical Practice Pre-Inspection Information Package'. An electronic copy of this document can be found at: https://oicronca.box.com/s/wm2dmulsej8koq4hxw13hynb4h9a2fld
This package contains FAQs and helpful checklists which have been adapted for this guidance document (Appendices 2 & 3).

Information on clinical trial site inspections performed in Canada is published in Health Canada's Drug and Health Product Inspections Database at: http://healthycanadians.gc.ca/drugs-products-medicaments-produits/inspecting-monitoring-inspection-controle/inspections/index-eng.php

It is also helpful to review previous Health Canada Annual Inspection Summary Reports. Previous fiscal year reports are available at:
https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/compliance-enforcement.html

The notice of inspection may also include an inspection plan, depending on the type of inspection and whether you're a participating site, Sponsor or other.

Preparation of the Study Team Guidance

Prior to the inspection visit, the research team should thoroughly review the study protocol and any study-specific procedures. It is helpful to have a pre-inspection meeting(s) with key study personnel to discuss any issues that have been identified. *See Appendix 1 – Prior to Inspection Visit.*

If you have a Quality Assurance (QA) team, a pre-inspection readiness review should be conducted separately or in conjunction with the Sponsor representative, if applicable.

Mock interviews can be conducted to help prepare research personnel to answer questions from the Health Canada Inspector. The research team should also review the List of Do's and Don'ts (*See Appendix 8 – Do's and Don'ts).* This list provides helpful tips for conduct during the inspection visit.

Checklist:

☐Arrange for pre-inspection visit(s) by Quality Assurance team, if applicable and as per institutional processes.

☐Review Health Canada's pre-inspection information (e.g. GUI-0100, GUI-0043…)

☐Review the study protocol and any study-specific procedures

☐Conduct pre-audit meeting(s) with key study personnel to discuss any issues that have been identified

☐Review monitoring plan for risk-based items and ensure the monitoring plan has been followed and corrective actions and preventative action (CAPA), if any, are implemented

☐Conduct a mock interview to help prepare research personnel to answer questions (ask question in a form that addresses the following areas: why, who, what, when and where)

☐Review the List of Do's and Don'ts *(See Appendix 8 – Do's and Don'ts)*

Study Document Preparation (*Also See Appendices 2, 3 and 7)*

Checklist:

☐ Assemble and organize study documents in a format to facilitate the inspection type (in person or virtual). Follow any Health Canada provided guidance with regards to virtual inspections, the processes in place and acceptable electronic tools/systems and methods of transfer of such documents.

☐Identify documents that will need to be copied, scanned for electronic submission

☐All source documents e.g., research participant records, pharmacy records, all signed informed consent forms are present.

☐Ensure availability of all health records for all enrolled research participants (ensure access is granted to the EMR as per institutional policies)

☐Any Data Clarification Forms (DCFs)

☐All study-specific SOPs and site/institutional SOPs, as applicable

☐Hospital equipment used in the study: maintenance and calibration records

☐Study specific electronic systems: validation records

☐Other: _____

Review all study documents for content, accuracy, legibility, traceability (version dates), attribution, timeliness (contemporaneous) and completeness:

☐ Investigator Site File and/or Sponsor File (ICH-GCP section 8 "Essential Documents for the Conduct of a Clinical Trial") and obtain any missing documents

☐ Study personnel's CV, qualifications and research training documentation, including any vendors and third party service providers (e.g., CRO's), QI

☐Documentation of any protocol-specific training and Sponsor SOPs

☐Study Task Delegation Log and have the QI correct any errors by initialing and dating the change. (e.g. complete prior to conduct of trial)

☐Study-required training was completed before the research staff member was delegated any protocol-specific task(s) or were given access to study information/database

☐All participant/patient logs are up-to-date (screening, enrollment, master log)

☐Correct version of the ICF was used and all completed ICFs have been signed and personally dated by the research participant/legally acceptable representative, witness (if applicable), and person obtaining consent

☐Source documents for sign-off of all study-related medical decisions by the QI or designated Medical Doctor (MD) Sub/Co-Investigator

☐Protocol Signature Pages for the site

☐All CRFs. Ensure sign-off by the QI, as required and as per Sponsor requirements

☐ Investigational Product Accountability records

☐All serious adverse event reports and serious unexpected adverse drug reaction reports (SU-ADRs), if any

☐Protocol deviations have been addressed, reported and documented accordingly

☐ If protocol deviations not previously reported are identified during the pre-inspection audit, document any CAPA and report to the REB as required.

☐All correspondence (for example Sponsor/REB)

☐ Clinical Trial Agreement specifically the QI's obligations and contracts e.g., service agreement, data transfer agreement and material transfer agreements,

☐Ensure all financial information, personnel records, audit reports, etc. are stored separately (*as per section GCP 5.19.3 Auditing Procedures: "To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings."*

☐Review (other):_____

☐Review (other):_____

<u>Document and resolve any discrepancies detected prior to the inspection visit.</u>

DURING THE INSPECTION VISIT

Day 1 of Inspection

Checklist

Prior to arrival for an on-site inspection:

☐Ensure that any rooms used for inspection and any facilities to be inspected are tidy before use, and the door must lock. Anytime a Health Canada Inspector leaves the room, ensure to lock the door.

☐Affix the Room Sign to any rooms to be used for the duration of the inspection

Upon Arrival:

☐Meet and escort the Health Canada Inspector to meeting room(s) and during any facility tour(s)

☐Provide the Health Canada Inspector with Visitor Identification, access to any database, EMR (as per institutional approvals and process)

☐ Bring attendance record (*See Appendix 9 – Attendance Record)*

☐ Arrange for someone to take notes during the meeting, and circulate meeting minutes after the meeting.

☐ Provide agenda of the day's events

Opening Meeting

The on-site inspection visit usually begins with an Opening Meeting conducted by the Compliance Specialist. For virtual inspections, provide link to all team members and the Health Canada Inspector in advance. Ask for advance notice as much as possible to set up meetings and understand during the week who the Health Canada Inspector wishes to meet with. All staff, departments and investigators should make themselves available during the week of the inspection.

Research team member should complete an attendance record (*See Appendix 9 – Attendance Record*).

In addition to the QI and key research team members, representatives of the following may also attend this meeting:

- Study Sponsor (this is actually a requirement if not for the entire session, at least to be available as needed)

- Other department/institutional representative (i.e., quality personnel or administration) – depending on the nature of the inspection
- Research Pharmacy
- Biomedical or clinical engineer (equipment maintenance) Clinical and/or Research Laboratory
- Health Records department
- Information Services (tech support, EMR support)
- Other key service providers

The Health Canada Inspector may present (or the QI should request to view) their Health Canada badge and their business card at the start of the Opening Meeting. Research team should document badge number. Following the introduction of the attendees, the Health Canada Inspector may explain the scope and purpose of the inspection and begin to collect site and study-specific information from the QI.

At the end of this meeting, the Health Canada Inspector and the research team should confirm the inspection visit schedule and discuss logistics. Ensure study staff are available during the time that the Health Canada Inspector is conducting the inspection as they often require assistance navigating the study documents and institutional policies. Throughout the inspection visit, only provide documents that are requested by the Health Canada Inspector.

The Health Canada Inspector may request a tour of any areas where the trial was conducted. For example:

- Any study drug storage areas i.e., Research Pharmacy
- Local laboratories, i.e. Core Laboratory and/or Research Laboratory
- Patient care areas
- Records storage areas

The Health Canada Inspector should be accompanied by a research team member during all tours. If a QA team member is available they should also join.

<u>Daily Debrief Meeting</u>

The Health Canada Inspector may identify observations throughout the inspection visit. Request a debriefing of the observations made by the Health Canada Inspector at the end of each day. This is also an opportunity to provide any clarifications, requested documents and answer questions, if possible. It is helpful to make notes during all debrief meetings (*See Appendix 10 – Summary of Inspection Observations – Daily Report).*

A separate research team debrief meeting is recommended as well. This meeting will allow the team to review and/or plan to complete outstanding requests from the Health Canada Inspector, discuss themes that are arising from questions the Health Canada Inspector is asking (may provide insight on direction of inspection) and ensure availability of team for the next day's work.

Photocopies or Sending Documents Electronically

During the inspection, always make two copies of each requested document - one for the Health Canada Inspector and reserve one copy for the QI. (Note: Industry Sponsors usually request a copy of all copied documents as well; making copies for the Industry Sponsor is best done at the end of the inspection visit. identifiable personal information **must not be given to the Sponsor**.)

- Stamp each copy of a document as a 'copy' and 'confidential'
- For any requested documents containing identifiable personal information, it must be redacted before giving the copy to the Sponsor
- If the Health Canada Inspector requests documents containing identifiable personal information, review your informed consent form and consult with your Research Ethics Board
- Maintain a daily record of the copies or documents sent electronically that are given to the Health Canada Inspector on the Document Release Log (*See Appendix 7 – Document Release Log*)
- For documents provided electronically through a virtual platform, keep a copy of the documents uploaded on the site's personal secure drive, with record of the date of upload to the virtual platform.

Areas of Focus

The Health Canada Inspector may review any or all of the following Health Canada documentation:

Study Regulatory Documentation

- All Health Canada authorization(s) and all correspondence with Health Canada and the Sponsor
- Research Ethics Board Attestation (may be included in REB approval letters)
- Qualified Investigator Undertaking Form for the site (should be signed by the site QI prior to the start of the study)
- Clinical Trial Site Information Form(s)
- Biologic Drugs Lot Release Fax-Back Forms (if applicable)

Research Ethics documentation

- All research ethics approvals
- All research ethics renewals
- All research ethics correspondence
- REB composition, specifically at key decision time points (to determine compliance with Division 5 requirements)

Training and Task Delegation Log documentation

- Institutional required up-to-date CVs of each site investigator
- Up-to-date resumes or CVs of key research team members
- Up-to-date resumes or CVs of Vendors and their training, as well as contracts in place
- Proof of current licensure for all research team members who are health care professionals, e.g. MDs, RNs, pharmacy technicians, respiratory therapists, dieticians, etc.
- Up-to-date training in ICH GCP and Division 5
- Determination of QI/PI appropriate delegation of all study-specific tasks appropriately.
- Up-to-date delegation log; late entries or discrepancies explained
- Clinical Trial Agreement (CTA) to determine if delegated study activities have been clearly articulated in the study contract.
- Training on the study protocol and specific study procedures to assess the adequacy and appropriateness of the training. Examples of acceptable documentation of training include, but are not limited to:
    - Slide decks: Note – All contributors listed in the slide deck are listed in the protocol.
    - Meeting agenda/minutes, including a list of all attendees
        - Sign-off sheets/certificates for training in the study protocol, study-specific procedures, any study amendments, etc.

Protocol Adherence

Assessment of processes and procedures in place to assure that all aspects of the trial are conducted in accordance with study protocol, any written SOPs, Division 5 and ICH GCP.
Assessment of the QI's involvement with the trial, specifically the documentation of all study-related medical decisions by the QI or a designated MD Co-Investigator. Examples of documentation that may be reviewed include, but are not limited to:

- Inclusion / exclusion checklist
- Study drug orders
- Medical examinations
- Clinic notes
- Assessment of study laboratory and/or test results
- Assessment of adverse events
- Safety management plan (to be provided by the Sponsor)

The Health Canada Inspector may also review the following:

- Written procedures for the recruitment and consent of research participants
- Harms and benefits section of the informed consent form(s) to ensure that research participants are informed of all potential harms and risks of the investigational product

- 100% of the signatures on the consent form for each enrolled research participant
- Written procedures for adverse event reporting
- All serious adverse events/serious adverse drug reactions, if any, which have been reported to the Sponsor, REB and/or Health Canada and assess adherence to the reporting timelines
- All protocol deviations, if any, which have been reported to the Sponsor, REB and /or Health Canada and assess adherence to the reporting timelines
- Data Safety Monitoring Board (DSMB) reports, and submissions to the REB

Record Handling

- Research participants' source data i.e., health records, notes of telephone calls, test results, questionnaires, research notes, etc., to verify the accuracy of the data reported on paper and/or electronic Case Report Forms (CRFs).
- A data source guide is required in order to navigate where data are located and in what format.
- Timelines for reporting study data to the Sponsor.
- All records should be readily available. All study essential documents should be kept securely for 15 years).
- Any institutional policies regarding records retention and storage.

Investigational Product (IP) Handling

The Health Canada Inspector may review the area where the investigational product (IP) is handled and stored, e.g. the site's Research Pharmacy. Ensure that the Research Pharmacy has a copy of all:

- Approved study protocols
- Investigator's Brochure(s)
- IP Handling procedures
- Randomization and emergency un-blinding procedures (as applicable)
- Randomization codes and the process for review by the Sponsor, as well as the secure means in which they are sent to sites.
- Copy of NOL
- Pharmacy manual

Pharmacy staff involved in the trial

- Evidence of training in the study protocol, study-specific procedures and any amendments.

Transportation, monitoring, disposition, storage, return and destruction of the IP

- All shipping records to ensure that the IP was maintained at the recommended temperature range while in transit
- IP label to ensure that it contains all elements listed in Division 5, C.05.011

- Documentation to ensure that the site handles and stores the IP under conditions which are secure, segregated and temperature-controlled
- Documentation of any temperature excursions
- Overall and individual study drug accountability records
- Control and traceability of the IP if the IP is moved from the main pharmacy to research storage location., and documentation of the same.
- IP quarantine SOP/procedures
- Sponsor process to release for dispensing or destruction

Study Equipment

Maintenance and calibration records of any study-specific equipment used for the trial, if applicable. Proper maintenance of the equipment is considered critical to research participant safety and the validity of data collected in the clinical trial. Each piece of study equipment should have documentation of:

- Name of Manufacturer and date of purchase
- Model Number and Serial Number
- Operating instructions
- Service agreement with third party vendor (if applicable)
- All calibration reports
- All maintenance reports (default is yearly) (dependant on Sponsor and Institution)
- Any service repair records

Study Biological Specimens Handling

The Health Canada Inspector may request to review the area where study biological specimens are processed and/or stored, usually the local Core and/or Research Laboratory, if applicable. Ensure that the local laboratory(ies) has a copy of all approved study protocols and laboratory study procedure manuals, as applicable.

- Laboratory staff training on study protocol, study specific procedures, and amendments
- Certification / accreditation / validation records for each laboratory used in the study
- Documentation to assess if study biological specimens have been collected, processed and shipped (if applicable) according to the study protocol and any study-specific procedures
- Maintenance and calibration records of all laboratory equipment used for the trial
- Storage of study biological specimens
- Documentation of any temperature excursions

Study Monitoring

The Sponsor, or QI/Sponsor for PI-initiated trials, is required to monitor the trial at all sites to verify that Division 5 requirements are met at each site and the trial is being conducted according to the principles of ICH GCP.

- Study Monitoring Plan
- Monitoring Log and visit frequency to assess the adequacy of monitoring by the study Sponsor.
- Site Initiation Monitoring Report and other Monitoring Reports, as necessary.
- Monitor details (e.g. who is it, CV, records of training like GCP, Health Canada Part C Division 5)

MEETING WITH PRINCIPAL INVESTIGATOR/QUALIFIED INVESTIGATOR

The Health Canada Inspector may request a meeting with the PI/QI to confirm the Investigator has a good oversight and knowledge of the trial. A good practice is for the Investigator to review the entire trial. Examples of areas of review may be:

- Qualifications of the Investigator – experience with clinical trials with drugs/medical devices
- Impression on how the trial was run
- Education provided about the study
- Training provided – Investigator's meeting, informed consent, protocol
- Sponsor's confirmation that site had SOPs in place
- Source documentation
- Protocol deviations – reporting, documentation
- Delegation Log, monitoring plan, overview of trial status

CLOSING MEETING - END OF THE INSPECTION VISIT

Prepare an attendance record (*See Appendix 9 – Attendance Record*) for this meeting. The QI and the research coordinators must attend this meeting. In addition, representatives of the study Sponsor, institutional representatives, research pharmacy, clinical and/or research laboratory and health records department (and other key service providers) may also be invited to attend.

At the Closing Meeting, the Health Canada Inspector may review the scope and purpose of the inspection, give a summary of the inspection activities and provide an explanation of Health Canada's risk ratings. The Health Canada Inspector may provide the QI with a verbal summary of the observations made during the inspection visit. This is also an opportunity to discuss the observations, request/provide clarifications and supporting documentation, as needed, and also to ask questions. It is helpful to make notes of all observations given by the Health Canada Inspector and any discussion.

The Health Canada Inspector may outline the next steps in the inspection process and provide a tentative timeline for the issuance of the draft Inspection Exit Notice.

AFTER THE INSPECTION VISIT

<u>Inspection Exit Notice</u>

The Inspection Exit Notice includes information such as: site profile, name of site officials, protocol title/number and name of investigational product used in the trial. The report will be written in such a way as to protect personal identity.

Each recorded observation is assigned a risk in accordance with *GUI-0043 - Classification of Observations Made in the Conduct of Inspections of Clinical Trials.* The risk categories are: Critical (Risk 1), Major (Risk 2), Minor (Risk 3). The draft Inspection Exit Notice also includes the overall inspection compliance rating of:

- **Compliant** – activities conducted are in compliance with Food and Drugs Act and it's associated Regulations; only minor and major observations reported
- **Non-Compliant** – activities conducted are not in compliance with Food and Drugs Act and it's associated Regulations; one or more critical observations; or several major observations that are deemed to be systematic issues

<u>Exit Meeting</u>

The Health Canada Inspector is required to schedule the exit meeting within 3 weeks of the last day of the inspection and provide the draft report 48 hours before the exit meeting. The Exit Meeting may be face-to-face, teleconference or virtually.

Prepare an attendance record (*See Appendix 9 – Attendance Record*) for this meeting. The QI, the research coordinators, and the institution's QA representative (if exists) must attend this meeting. In addition, representatives of the study Sponsor, institutional representatives,

research pharmacy, clinical and/or research laboratory and health records department (and other key service providers) may also be invited to attend.

The Health Canada Inspector will review the draft written Inspection Exit Notice with the QI. If necessary, any corrections, clarifications and/or revisions may be made to the draft report. The Health Canada Inspector may outline the next steps in the inspection process regarding the issuance of the Final Inspection Exit Notice (inspection report that outlines any observations (deficiencies/deviations) noted) and the timeline for the QI and Sponsor's response to the Final Exit Notice (usually thirty (30) calendar days).

Inspection Follow-up

With the receipt of the Final Inspection Exit Notice, the QI and or the Sponsor should carefully prepare a formal written response to all observations with an 'open' status, including corrective and preventative action (CAPA) plans. The full response should be submitted to the Health Canada Inspector within the required time period. Documents to show evidence of corrective and preventative action should be submitted with the response. If the Health Canada Inspector has additional questions, a follow-up letter will be issued to the site with information on which observations still require additional follow-up. The QI and sponsor will need to prepare a formal response to the observations that remain open and submit it within the required timeframe.

When all responses have been reviewed by Health Canada and when no further actions in response to the observations are required, the Health Canada Inspector issues a written acknowledgement to the QI and Sponsor and the inspection cycle is closed. The QI should file all documents pertaining to the inspection confidentially and separately from the site trial files.

REFERENCES

Health Canada's POL-0001: Compliance and enforcement policy for health products

Health Canada's POL-0030: Compliance and enforcement approach and inspection strategy for clinical trials of drugs involving human subjects

Health Canada's POL-0138: Policy on accessing the premises of a regulated party remotely to verify compliance

Guidance Document: Classification of observations made in the conduct of inspections of clinical trials (GUIDE-0043)

Health Canada's Food and Drug Regulations

Government of Canada, Medical Devices Regulations, Part 3 Medical Devices for Investigational Testing involving Human Subjects, SOR/98-282, May 7, 1998; last amended March 2, 2022, current to September 22, 2022.

Guidance Document – Annex 13 to the Current Edition of the GMP Guidelines: Drugs Used in Clinical Trials (GUI-0036)

Good manufacturing practices inspection policy for drug establishments (POL-0011)

Government of Canada, Natural Health Products Regulations, Part 4 Clinical Trials Involving Human Subjects, SOR/2003-196, June 5, 2003; last amended June 21, 2022, current to September 22, 2022.

Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100)

Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

Good Clinical Practice Pre-Inspection Information Package

"Health Canada's GCP Compliance Program", ACRP Canadian Chapter Webinar, presented Dec. 05, 2012

"GCP Compliance in Canada: Division 5 and other Requirements", SoCRA Annual Meeting, Orlando, Florida September 2014

Network of Networks, SOP017_09 Audits and Inspections

SOP# QA601.004- External Audits and Inspections, Cancer Clinical Research Unit, Princess Margaret Hospital (effective 29Mar13)

LIST OF APPENDICES

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APPENDIX 1 - PRIOR TO INSPECTION VISIT

1. <u>Inspection Notification</u>

A. Health Canada Inspector initially notifies the Qualified Investigator (QI)/ Clinical Trial Site and/or the Sponsor of the inspection visit (by phone and/or email).

Date of notification: _____

B. Confirm the following information with the Health Canada Inspector:

☐Name and contact information of the Health Canada Inspector:

_____

☐Name of the Qualified Investigator

☐Study Title and Protocol Number *(if applicable)*

☐Original Health Canada Control Number: _____

☐Purpose of the inspection: *(circle one)* Routine or For Cause

☐Current Study Status: _____

☐ Inspection Plan area of review provided in Health Canada's letter of inspection. Possible areas of inspection are:

- ☐Pharmacovigilance
- ☐Computerized Systems – e.g. eCRF/IWRS/IVRS, REDCap, Cerner/PowerChart Validation, User Acceptance Testing
- ☐Monitoring
- ☐Data Management
- ☐Trial Master File
- ☐Standard Operating Procedures
- ☐Clinic areas involved in the care of trial participants
- ☐Hospital/clinic equipment used in the collection of critical trial data
- ☐Other: _____

☐Tentative Inspection Start Date:_____

☐Arrival Time/Location (if onsite). Time of virtual meeting, and mode of virtual meeting.

Describe connection details:

_____

☐Tentative Inspection End Date:_____

☐Who the Health Canada Inspector expects to be present during the Opening Meeting:

☐QI ☐Sponsor ☐Study Coordinator(s) ☐Other: _____

☐ Health Canada Inspector's specifications (space, computer, phone, internet, directions, etc.)

_____

☐Health Canada's *Notice of Inspection Letter*. Receipt Date: _____

C. Notify the following people as soon as possible: *(Designate a Main Coordinator for the Inspection)*

☐Sponsor representative(s) *(if applicable)*

☐ Arrange pre-inspection visit by the Sponsor representative(s) as soon as possible (plan for at least 2 days on-site or virtually as per institution processes and policies). Enable a secure teleconference line for the week as well, as not all virtual meetings need to be conducted using video.

☐Research Ethics Board (REB) of Record

☐Institutional authorities

☐Institution's research quality assurance department *(if applicable)*

☐All relevant personnel, including sub-investigators, study coordinators

☐All relevant hospital departments *(as applicable, add additional checkboxes as needed)*

☐Health Records ☐ Research Pharmacy ☐Core Laboratory

☐Biomedical Engineering ☐Electronic System Support ☐Other:_____

2. <u>Logistics for an Onsite Inspection</u>

☐Record all time and expenses related to the inspection

☐Arrange for an ID badge/ Visitor pass*)*, WiFi and network access(as per institution-specific process

☐Arrange for a private secure room that meets the Health Canada Inspector's specifications. Secure or remove documentation that is not related to the inspection.

Room: _____

☐Prepare a sign for the room *(Appendix 4)*

☐Arrange a teleconference line, or other virtual platform for inspection dates (e.g., Zoom)

☐Arrange for laptops and any A/V equipment required for onsite or virtual meetings, access to any database, Electronic Medical Record (EMR) *(as per institution-specific process).* If possible ensure that the option to change password is provided to show security. Ensure to remove all access immediately after the inspection. Set to end of day on the last day of the inspection.

☐Obtain any study-related documents stored off-site, as applicable

☐Initiate a Study Contact List (examples CRO's or vendors, staff, site qualified investigators, department contacts) *(Appendix 5)*

☐Have Source Location Locator, or similar navigation reference document readily available *(Appendix 11)*

☐Locate a nearby photocopier and assemble stationary supplies for making photocopies

☐Prepare a Document Release Log *(Appendix 6)*

☐Prepare Attendance Record(s) *(Appendix 8)*

Additional Logistics for a Virtual Inspection

☐Select a virtual platform (e.g. MS Teams, SharePoint) to meet the needs of the inspection: Zoom, teleconference line, WebEx, etc. Ensure adequate staff with the expertise to ensure the smooth flow of using virtual technologies. Ensure passwords and login for these systems are secure and disseminated in a secure manner.

☐ Check to see if break out rooms are required.

☐Check re: institutional policies and procedures, and other requirements such as REB, Privacy, consent forms with regards to remote access to source data via electronic platforms as per applicable to the centre (e.g., EMR, REDCap Send-it) email of study documents, and other (e.g. EMR/Technical Support staff, etc.)

☐Health Canada's Inspector will provide a virtual agenda to the Sponsor-Investigator/Investigator along with any revisions prior to visit. .

☐Provide the Health Canada Health Canada Inspector with virtual platform information, log-ins and password details *(as per institution-specific process)*

☐ Scan any paper documents that have been requested for a virtual inspection

☐ Ensure scanner is available for scanning of paper documents for upload during the inspection

APPENDIX 2 - CLINICAL TRIAL INFORMATION REQUEST FORM

Qualified Investigator (Last name, First name)	
Contact Information (phone and fax numbers, mailing and email addresses)	

Title of the Protocol For the Clinical Trial	**Protocol Number**	**Currently enrolling? (Y/N)**	**First date of dosing**	**Sponsor***	**CRO and/or SMO details (if applicable)**	**Drug Name And Dosage form**	**Phase**	**Number of Participants Enrolled, Withdrawn, Still Active**	**Number of SAEs and/or ADRs at site**

* This is for informational purposes only. Health Canada will provide this document for sites to complete. The sponsor is the individual, corporate body, institution or organization that applies to Health Canada for authorization of a clinical trial and is responsible for the overall conduct of the trial. The term is not limited to commercial sponsors; it also applies to independent investigators who are self-sponsored. If the sponsor is foreign / international, please include Canadian representative for foreign sponsor (if known).

APPENDIX 3 - HEALTH CANADA INSPECTION DOCUMENT CHECKLIST

Health Canada Pre-Inspection Package - Good Clinical Practices- Inspection Document Checklist*

Study Title:_____

- ☐ Copy of the Study Protocol, including any amendments
- ☐ Copy of Informed Consent Form, including any amendments
- ☐ Copy of the Principal (Qualified) Investigator's declaration *[Qualified Investigator Undertaking Form]*
- ☐ Copy of Research Ethics Board attestation, if applicable (REBs only)
- ☐ Delegation of Responsibilities chart or list
- ☐ Research Centre Organizational Chart
- ☐ Investigator's CVs and Research staff résumés *[Auditor may request a copy of site QI's CV]*
- ☐ Standard Operating Procedures (e.g., informed consent process, adverse drug reaction reporting, training, etc.)
- ☐ Training records *[study staff training on study protocol & amendments, study-specific procedures, GCP, Division 5, etc.]*
- ☐ Correspondence files between:
    - Sponsor and Health Canada *[confirmation of document transmission b/t Sponsor / Health Canada / site(s)]*
    - Sponsor and the site (e.g., Qualified Investigator, Contract Research Organization, if applicable - this would include Sponsor monitor reports, etc.)
    - Site and Research Ethics Boards (e.g., approval of protocol, amendments, Informed Consent Form, advertising, etc.)
- ☐ Adverse Event and Serious Adverse Event documentation (e.g., list, reports, etc.)
- ☐ Investigational Drug Accountability Records
- ☐ Service providers' contracts (e.g., internal/external clinical/research laboratories, Research Pharmacy, drug supplier, storage, equipment, etc.)
- ☐ Records of calibration, maintenance and temperature monitoring for the applicable research equipment *[separate binder]*
- ☐ Investigator Brochure(s) or Product Monograph(s), as applicable *[Drug Safety Information]*
- ☐ Source data (e.g., Informed Consent Forms, pharmacy records, participant medical records, etc.) *[original hard copy]*
- ☐ Case Report Forms
- ☐ Participant Enrollment Log

* It should be noted that this list is not all inclusive, and is not provided in any order of priority; additional documents may be requested prior to and/or after the inspection. In addition, some of the above documents may not be applicable in all cases. For additional guidance, please refer to the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practices which can be found at *https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html*.

APPENDIX 4 - HEALTH CANADA INSPECTION PLAN CHECKLIST

Health Canada Pre-Inspection Package - Good Clinical Practices - Inspection Plan Checklist*
Study Title: _____

- ☐ Identify the key study personnel and their delegated responsibilities, and review their education, training and experience. *[make sure each role matches the delegation log]*
- ☐ Review the correspondence with Health Canada and the Research Ethics Board (REB) to ensure that the REB has provided written approval of the protocol, the Informed Consent Form (ICF) and other information provided to the participants before the trial begins, to verify the REB has approved every amendment to the protocol and Informed Consent Form. Ensure the information provided to Health Canada is consistent with what the REB approved.
- ☐ Review the procedure for obtaining informed consent and ensure that the statements of risks and benefits in the Informed Consent Form are consistent with those required by Health Canada and the REB.
- ☐ Verify that the Informed Consent Form used to administer informed consent is the correct version (e.g., the most recently approved and in the appropriate language of the participant population) and is signed and dated by the participant or the participant's legally acceptable representative and by the person who obtained consent, before the participant is enrolled in the trial and verify this for all participants enrolled in the trial.
- ☐ Ensure that the investigator has adhered to the protocol/amended protocol that has been approved by Health Canada and the REB. Verify, for instance, that the participants were selected in accordance with the inclusion / exclusion criteria, drug dosages are administered in accordance with the protocol, use of concomitant medications is documented, data with respect to safety and efficacy are documented and criteria for removal of participants from the study are followed, etc.
- ☐ Verify that the data has been accurately transcribed from source documents (e.g., original medical records) to electronic case report forms. *[Verification plan]*
- ☐ Verify that the data has been accurately transcribed from the paper case report forms to the study electronic database (if applicable). Confirm the sponsor's validation plan of the study electronic database.
- ☐ Ensure that all adverse events are documented and that adverse drug reactions are reported in accordance with the protocol and regulatory requirements. To do so, verify records to assess the timeliness, accuracy and completion of all required reporting. *[process for handling SAEs]*
- ☐ Verify that adequate supervision of medical care by the qualified investigator is documented
- ☐ Ensure that the investigational drug(s) is labeled in accordance with Section C.05.011 of Division 5 of the *Food and Drug Regulations*
- ☐ Ensure that all quantities of all lots are reconciled by checking records for drug receipt at the site, dispensing records, returns to sponsor, etc.
- ☐ Verify that the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices, protocol and labelling requirements.

Continued on next page…

CONTINUED
APPENDIX 4 - HEALTH CANADA INSPECTION PLAN CHECKLIST

Health Canada Pre-Inspection Package - Good Clinical Practices - Inspection Plan Checklist*
Study Title: _____

- ☐ Verify that the test samples for clinical testing (if applicable) are handled in accordance with the protocol.
- ☐ Review sponsor monitoring reports or correspondence with the sponsor/monitor to ensure that all monitor findings are documented and corrected.
- ☐ Review sponsor monitoring reports or correspondence with the sponsor/monitor. All monitor findings should be documented, as well as the action(s) taken to correct them.
- ☐ Confirm if there are provisions for records to be retained for 15 years.
- ☐ Ensure there is an updated organizational chart available
- ☐ Ensure calibration for all research equipment are available and up to date

* The above represents an example of areas a Health Canada Inspector may focus on during an inspection. It should be noted that the above inspection plan is not all inclusive, and is not provided in any order of priority; it could vary depending on the type of site and/or clinical trial inspected, etc. For additional guidance, please refer to International Conference on Harmonization (ICH) guideline E6: Good Clinical Practices which can be found at *https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html*

APPENDIX 5 - ROOM SIGN

Quiet Please

Health Canada Inspection in Progress

Month day to day, year

Only those involved in the inspection will have access to this room during this time

APPENDIX 6 - STUDY CONTACT LIST

Study Contact List

Protocol Title:	
Protocol Number:	
Principal Investigator/Qualified Investigator:	
Date(s) of Inspection Visit:	

Name	Location / Dept.	Office Number	Best Contact Info (i.e., cell #, pager)	Availability

APPENDIX 7 - DOCUMENT RELEASE LOG

DOCUMENT RELEASE LOG
Health Canada Inspection

Protocol Title:	
Principal Investigator / Qualified Investigator:	
Date of Inspection Visit:	

No.	Inspector	Date of Release	Document Requested During Inspection	Document Version Date (if applicable)	Reason	Reviewed During Inspection (yes or no)	Retained by Health Canada Inspector (yes or no)

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APPENDIX 8 - DO'S AND DON'TS

Here are some general dos and don'ts during interviews with the Health Canada Inspector:

Do

- Be nice - provide a quiet, comfortable, temperature-controlled environment
- Be honest, polite, cooperative
- Be direct, factual, brief, precise
- Be professional, confident and relaxed - you are the expert
- Be sure that you understand the question - ask for clarification, if necessary
- Only answer within one's expertise - seek an expert, if needed
- It is OK to say "I don't know. I will get back to you."
- If you need time to get information or documentation then say so - provide a time estimate - Health Canada Inspectors do not like to wait without a reason
- If you promised something to the Health Canada Inspector, then do not forget and do not delay
- Make a list of requested documents and questions
- Be sure it is the right document before releasing it
- Ask for clarification of audit findings, if necessary, but do not debate the merits of the findings
- Document everything

Don't:

- Take it personally
- Guess at answers - if uncertain, defer the response until you obtain the correct information
- Ask unsolicited questions, hypothetical questions, delay to requests
- Become defensive
- Express a personal opinion
- Offer extra information
- Point out a fault
- Extend a discussion by asking further questions

Never:

- Reply for someone else
- Say "never"!
- Give the Health Canada Inspector more than they ask for
- Argue with the Health Canada Inspector
- Promise anything on the spot
- Mislead the Health Canada Inspector or give wrong/incorrect information

Tips:

- Do not interpret the Health Canada Inspector's question(s)
- Be careful when answering questions such as:
- "What do you think?"
- "How often does this happen?"

APPENDIX 9 - ATTENDANCE RECORD

ATTENDANCE RECORD	☐ Opening Meeting	☐ Closing Meeting
	☐ Exit Meeting	☐ Other, Specify: _____

Protocol Title:	
Principal Investigator / Qualified Investigator:	
Name of Health Canada Inspector:	

Date:	
Time:	
Location:	

Print Name	Signature	Study Role

Page _____ of _____

APPENDIX 10 - SUMMARY OF INSPECTION OBSERVATIONS – 'DAILY REPORT'

Protocol Title:	
Principal Investigator (PI) / Qualified Investigator (QI):	
Name of Health Canada Health Canada Inspector:	
Inspection Date Range:	
Inspection Day (i.e., Day 1):	
List of Attendees (if applicable):	

No.	Related to (i.e., Name of Document)	Observation	PI/QI Response / Action Item (if applicable)	Health Canada Determination (Acceptable or Unacceptable)

No.	Related to (i.e., Name of Document)	Observation	PI/QI Response / Action Item (if applicable)	Health Canada Determination (Acceptable or Unacceptable)

Page _____ of _____

APPENDIX 11 – POTENTIAL HEALTH CANADA QUESTIONS

1. How many trials is the PI/QI currently working on and describe each one
2. How many people are involved in the trials (i.e. how many sub-investigators and coordinators)?
3. Who is responsible for obtaining Informed Consent (IC)?
4. Who is responsible for assessing Inclusion/Exclusion criteria?
5. Who assess/obtains medical history?
6. Who actually examines the participant?
7. Who randomizes the participant?
8. Who administers the drug?
9. Who enters the eCRF data?
10. Who takes care of drug storage and accountability?
11. How was the training delivered?
12. Was there an investigator meeting? How was the protocol reviewed with sub-investigators?
13. Is there any specialized training?
14. Who monitored the study?
15. Was the sponsor accessible during the study?
16. How often was the study monitored? Was there pre-study monitoring?
17. How did you recruit for the study? How were patients identified?
18. What is the date of first participant's IC and date of first dosing?
19. What is the date of the last participant's IC and the date of first dosing?
20. Do you have an ICF SOP?
21. Do you inform the participants GPs of participation? Is consent obtained to inform GP?
22. Is there any other information given to the participants?
23. Were there any screen failures or withdrawals?
24. What is the current version of the IB?
25. Were there any SAEs? SUAEs?
26. Who assessed the causality of the AEs?
27. Were there any safety reports?

Continued
APPENDIX 11 – POTENTIAL HEALTH CANADA QUESTIONS

29. What is your process for reporting SAEs to your REB, sponsor and Health Canada?
30. Were there any protocol deviations? If so, what were they?
31. Were the deviations reported to the sponsor?
32. Was the protocol clear and easy to understand (i.e. Tests, inclusion and exclusion, deviations)?
33. Did the participants have any issues complying with the protocol?
34. Were patients who regained consciousness re-consented?
35. Who sees the participants at study visits?
36. How is source documented?
37. What data requires "sign-off" from the PI/QI?
38. Where is the source data stored?
39. Is the office where the source is located locked?
40. Who enters eCRF data and who has access to data? Who can alter the data?
41. Has the database been validated, backed up and is there an audit trail in the eCRF?
42. Can you print from the eCRF?
43. Where is medication stored?
44. What is the "flow" of the study drug? Who is the importer of the drug?
45. Is there a drug accountability log maintained?
46. Is temperature of the drug recorded and is there an alarm if temperature deviation?
47. Is the temperature of the drug monitored while in transit?
48. Are there documentation that the drugs were manufactured, handled, stored, shipped and dispensed/administered/returned according to the protocol and the manufacturers requirements as approved in the HC CTAIs there any special equipment used for the study? Any equipment provided by the sponsor?
49. Who draws and prepares the lab samples? (i.e. How is the temperature monitored for samples held for batch shipment? How is the lab aware when to send batch shipments?)
50. Do you have a record retention SOP?
51. Where can I find the stability information for the drug?

Continued
APPENDIX 11 – POTENTIAL HEALTH CANADA QUESTIONS

Additional areas of interest may include:

- Routine meetings with staff to review trial progress, adverse events, and update staff on any changes to the protocol or other procedures.
- Routine meetings with the sponsor's monitors.
- A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study.
- A procedure for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments).
- A procedure for ensuring that the consent process is being conducted in accordance with ICH GCP and institutional requirements and that study participants understand the nature of their participation and the risks.
- A procedure for ensuring that source data are complete, accurate, contemporaneous, and original.
- A procedure for ensuring that information in source documents is accurately captured on the case report forms (CRFs).
- A procedure for dealing with data queries and discrepancies identified by the study monitor.
- Procedures for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements.
- A procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner.
- How are study staff who are not direct employees of the investigator overseen (i.e. pharmacist).

APPENDIX 12 – SOURCE DOCUMENT LOCATOR

GCP 8.1 The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

This document should be completed at the beginning of the study and updated regularly throughout the lifecycle of the trial. Section 8.0 of GCP is the minimum list of essential documents that are required for the conduct of a clinical trial. Please refer to Sponsor communication for the essential documents required for each trial. Any records/documents that are generated by the investigator /institution before, during and after the trial should also be included.

Study Title:	
Sponsor/CRO:	
QI Name:	
Responsible Person:	

Source/ Essential Document	**Location of Source/Essential Document During the Trial**	**Type of Media**	**Media & Location of Source/Essential Document Saved for 15 Years**
Before the Clinical Phase of the Trial Commences During this planning stage the following documents should be generated and should be on file before the trial formally starts			
INVESTIGATOR'S BROCHURE			
SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)			
INFORMATION GIVEN TO TRIAL SUBJECT **- INFORMED CONSENT FORM** (including all applicable translations) **- ANY OTHER WRITTEN INFORMATION** **- ADVERTISEMENT FOR SUBJECT RECRUITMENT** (if used)			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
FINANCIAL ASPECTS OF THE TRIAL			
INSURANCE STATEMENT (where required)			
SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)			
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion			
INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)			
CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)			
NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL			
MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)			
SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)			
INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)			
SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED			
DECODING PROCEDURES FOR BLINDED TRIALS			
MASTER RANDOMISATION LIST			
PRE-TRIAL MONITORING REPORT			
TRIAL INITIATION MONITORING REPORT			
During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available			
INVESTIGATOR'S BROCHURE UPDATES			
ANY REVISION TO: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)			
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol amendment(s) - revision(s) of: - informed consent form			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
- any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favourable opinion - continuing review of trial (where required)			
REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR: - protocol amendment(s) and other documents			
CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)			
UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL			
UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)			
DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS			
MONITORING VISIT REPORTS			
RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes - notes of telephone calls			
SIGNED INFORMED CONSENT FORMS			
SOURCE DOCUMENTS			
SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)			
DOCUMENTATION OF CRF CORRECTIONS			
NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS			
NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION			
INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)			
SUBJECT SCREENING LOG			
SUBJECT IDENTIFICATION CODE LIST			
SUBJECT ENROLMENT LOG			
INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE			
SIGNATURE SHEET			
RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)			
After Completion or Termination of the Trial After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following			
INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE			
DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION			
COMPLETED SUBJECT IDENTIFICATION CODE LIST			

Source/ Essential Document	Location of Source/Essential Document During the Trial	Type of Media	Media & Location of Source/Essential Document Saved for 15 Years
AUDIT CERTIFICATE (if available)			
FINAL TRIAL CLOSE-OUT MONITORING REPORT			
TREATMENT ALLOCATION AND DECODING DOCUMENTATION			
FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)			
CLINICAL STUDY REPORT			